Rejection Under §112, First Paragraph

The specification is objected to under 35 U.S.C. §112, first paragraph, as allegedly failing to describe and teach how to make and/or use the instant invention. Claims 1-6 and 8-9 stand rejected under §112, first paragraph for the same reasons. In maintaining this rejection, the United States Patent and Trademark Office ("USPTO") ignored applicants' response mailed May 3, 1994, and "cut and pasted" its reasons from the previous Action. This is plainly apparent in that the USPTO reiterates its allegation that:

> [t]he specification goes on to refer to proteins having "sufficient homology" without really providing the routineer with an exact definition of how such homology is to be determined. Without such guidance, undue experimentation would be required to determine which of the "substantially homologous" proteins fall within the applicants' disclosure. [Final Action, page 2, emphasis added]

As explicitly stated in applicants' response of May 3, 1994, neither of the phrases "suffic-ient homology" nor "substantially homologous" have been used in the instant application or claims. As such, specific definitions thereof will not be found in the application. The USPTO has ignored this fact entirely and is improperly reading language into applicants disclosure which does not exist. Applicants cannot respond to an objection of terms when such terms are not used in applicants' specification! Applicants respectfully request consideration of this fact, and thus withdrawal of the rejection since the basis for the rejection is erroneous and improper.

In addition, applicants object to the USPTO's use of the term "routineer" in the rejection. Nowhere is this term defined. This is not the statutory term for a person having ordinary skill in the art. Applicants reviewed Webster's Collegiate Dictionary for a definition of such term and was unable to locate same. Thus, applicants consider it to be an undefined term and indeed the term "routineer" implies that the level of skill is **less** than that of a person having ordinary skill in the art, thus requiring applicants to establish **more** than the statute requires. Proper use of "the person having ordinary skill in the art" or "ordinary skilled artisan" is respectfully requested.

Furthermore, the USPTO alleges that "undue experimentation would be required to determine which of the 'substantially homologous' proteins fall within the applicants' disclosure." Not only do applicants disagree with this statement, but it is clear that the USPTO has intermixed and confused the legal requirements of 35 USC §112. First, it must be reiterated here that the instant rejection is being made under §112, *first paragraph*. The USPTO's allegation also utilizes requirements of the second paragraph of §112. The basis for the rejection is not clear, and withdrawal or reversal of this rejection should be made for clarification. See, *In re Borkowski*, 164 USPQ 642 (CCPA 1970).

In order to expedite prosecution, applicants provide an a brief analysis of §112. The first paragraph of §112 contains three independent and distinct requirements: (1) to describe the manner and process of making and using the claimed invention in such full, clear, concise and exact terms as to enable one skilled in the art to make and use the invention. This is referred to as the "enablement requirement"; (2) to describe the subject matter defined in the claims in the specification. This is referred to as the "written description" requirment; and (3) to set forth the best mode contemplated by the inventor of carrying out the invention at the time of filing.

The second paragraph of §112 requires that : "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Thus, a claim that is understandable to one of ordinary skill in the art and that defines subject matter which applicants regard as their invention, meets the requirements of §112, second paragraph. In other words, all that is required by §112, second paragraph, is the claims set out and circumscribe a particular area which the applicants regard as the invention with a reasonable degree of precision and particularity. The claims are to provide a clear warning to others as to what constitutes infringement of the patent. See *In re Borkowski*, 164 USPQ 642 (CCPA 1970) wherein the Court held:

> [i]f the scope of the subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends that claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention.

Applicants' claims clearly satisfy the requirements of the two paragraphs. Indeed, it is unclear how and why a person of ordinary skill in the art would resort to "undue experimentation" in order to determine what constitutes *infringement* of the patent. It is important to note here that the USPTO has erroneously stated that it is the scope of "applicants' disclosure" that is the legal standard. In fact, the scope of applicants' invention is determined by the scope of the *claims* not the scope of their disclosure. In addition, why would the ordinary skilled artisan resort to any "experimentation" at all in order to determine whether his protein fell within the scope of applicants' claims? All the ordinary skilled artisan has to do is read and understand the specification and claims. Nothing more is required, and certainly laboratory experimentation is not required to determine the scope of the claimed subject matter.

At page 4 of the Final Action, the USPTO states that " a broad reading of the specification disclosed as 'variants' or 'derivatives' is not supported by sufficient intermediate disclosure to define all derivatives." Once again, the USPTO has read language into applicants' specification which does <u>not</u> exist. The term "variants" is nowhere used by applicants to describe its invention. Applicants request that the USPTO acknowledge that the

term "variants" is not recited in applicants' specification and remove such from the rejection. With regard to enablement of the claimed invention, the USPTO concedes; however, that the "disclosure is considered sufficient only for C terminal deletions up to amino acids 142." However, the USPTO alleges:

> random alteration of residues between amino acids 3 and 142 is not supported. Moreover, conservative substitutions are also not considered enabled without the practice of undue experimentation. Such a conclusion of enablement is reached because applicants have not disclosed a discrete assay to which provides an endpoint for the treatment. [emphasis added]

Thus, the USPTO has rejected applicants' claims on the *assumption* that a person having ordinary skill in the art at the time the application was filed would have been unable to assay his or her TNF antagonist for the claimed activity, without resorting to undue experimentation. The USPTO states that more than a binding assay is required here. It asserts that the required assay must show "*in vivo* functionality." Further, the USPTO states that "applicants' *in vivo* data is not conclusively correlated with a reduction in disease" [emphasis added]. The instant issue is whether the specification describes the manner and process of making and using the claimed invention in such full, clear, concise and exact terms as to enable one skilled in the art to make and use the claimed invention. The alleged insufficiency of applicants's data is irrelevant to the enablement requirement.

Without providing any scientific reasoning to support its assertions, the USPTO stated that even conservative substitutions were not enabled and would require undue experimentation. Applicants submit that conservative substitutions are routine in the art. The methodology is routine and well-characterized. The USPTO is reminded that in biotechnology, the level of skill in the art is very high, and that the case law is well-established on the point that while some experimentation may be required, and even if such experimentation is time-consuming, it may not involve "undue" experimentation. The USPTO is essentially stating that an inventive process will be required by the ordinary skilled artisan to make conservative amino acid substitutions. The USPTO has provided no reasoning to support this belief.

The USPTO also states that becuase the invention relates to a "method of treatment, not a product, which could have in vitro assays. Therefore, a different kind of endpoint must be established. *** applicants must provide a specific assay which has been correlated with the method of treament." [emphasis added]

Applicants disagree. It is not clear why the USPTO believes an assay is required to measure disease reduction. Indeed, the USPTO has provided no reasoning to support this statement. Applicants' disclosure provides clear methods for measuring reduction in disease. Indeed, for example, at page 29, Example 4, the reduction in knee-joint swelling is measured,

and histopathology scores determined. This is a simple and accurate means for measuring the reduction in disease. No separate in vitro assay, applicable for all diseases, need be established under §112. Moreover, the USPTO is required to provide specific reasoning as to why a physician in the art of treating arthritis would not be able to practice the claimed invention as it is described in the disclosure. Withdrawal of the rejection is requested.

Contrary to the USPTO's assertions, applicants are not required to disclose a conventional assay that proves the TNF antagonists function in vivo. Indeed, the USPTO is requiring applicants prove more than the statute requires. The USPTO requires "conclusive" proof of in vivo efficacy, whereas, it is clear that the law does not require such a high standard of proof. All that is required is that the data demonstrate a preponderance of the evidence in favor of the disclosed utility. That is, the data must lead one of ordinary skill in the art to believe the claimed invention is more likely than not to function for the disclosed utility. Proof beyond a reasonable doubt is reserved for criminal cases, not patent applications.

However, in an effort to expedite prosecution, and to further establish that applicants' statements of utility are credible, applicants submit a Declaration under Rule 1.132 by Dr. Moreland. Attached to Dr. Moreland's Declaration is a photocopy of a manuscript he prepared that provides experimental data from a Phase I clinical trial in humans that the claimed method possesses utility. Indeed, Dr. Moreland declares that the recombinant soluble TNFR:Fc fusion protein "is well tolerated" and the rheumatoid arthritis patients showed "trends of improvement in painful and swollen tender joint counts and biological indicators of inflammation (CRP)." Indeed, there was a 44% mean improvement in total pain and total joint scores for patients receiving sTNFR:Fc as compared to only a 22% improvement for patients receiving placebo. Additionally, average morning stiffness improved by 55% in the treated patients. The Westergreen erythrocyte sedimentation rate (ESR) decreased 32%, which was significant ($p < 0.05$). Finally, the C-reactive protein levels also decreased significantly (27%) in treated patients compared to placebo patients (13%). Clearly, the claimed method possesses patentable utility. Withdrawal of the rejection is requested.

Rejection Under 35 U.S.C. §102

Claims 1-6 and 8-9 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Brennan et al.

Applicants respectfully disagree with the rejection. As stated in applicants' May 3, 1994 response, it is axiomatic that in order for applicants' claims to be anticipated under §102, every element of the claimed invention must be present in a single prior art document. *In re Spada*, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990). This was not refuted by the USPTO.

Brennan et al. disclose that an anti-TNFα antibody inhibits synovial cell interleukin-1 production in patients with rheumatoid arthritis. However, applicants' amended claim 1 recites a Markush group of TNF antagonists, none of which is an anti-TNFα antibody. Therefore, it is clear that every element of the claimed invention is not present in Brennan et al. Withdrawal of the rejection is requested.

Rejection Under 35 U.S.C. §103

Claims 4-5 and 8-9 are rejected under 35 U.S.C. §103 as allegedly being obvious over Brennan et al. in view of Harris and Smith.

Applicants traverse the rejection simply because Brennan et al. cannot be combined with Harris et al. or Smith et al. since neither Harris et al. nor Smith et al. is available as a prior art reference. As discussed above, Brennan et al. should not have been cited against applicants' claims since claim 1 does not recite an anti-TNF antibody. Smith et al. was published May 25, 1990, which is after applicants' claimed priority date, and Harris et al., was also published May 3, 1990, which is after applicants' claimed priority date.

Applicants wish to address an issue raised in the rejection that is particularly disturbing to the applicants. It is stated in the Final Action that:

> The Brennan reference does not teach the use of TNF receptors. However, this is not considered significant because the TNF receptors of the instant claims and the anti-TNF antibodies of Brennan operate by the same mechanism. That mechanism is the binding of TNF... [emphasis added]

Obviousness under 35 U.S.C. §103 is based on a comparison of the prior art and the claimed invention. Indeed, the statute states:

> A patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art ....

In the instant rejection, the USPTO has improperly set its own standards of obviousness under §103. Nowhere do applicants read the statute as stating that a patent may not be obtained if the subject matter sought to be patented and the prior art "operate by the same mechansim" or achieve the same end result! Nowhere does the Patent Law require only one patent to be granted for a composition of matter that can accomplish a certain result. Indeed, the USPTO itself has granted myriad patents to compositions of matter as angiotensin converting enzyme (ACE) inhibitors, even though they all achieve the same end result, or "operate by the same mechanism" which is the inhibition of ACE, or the lowering of blood pressure.

In response, the USPTO alleges that applicants are not entitled to their claimed priority date since the earlier applications allegedly "did not contain any detailed enabling disclosure which would teach the routineer how to make and/or use the instant invention." Applicants disagree. At the outset, the USPTO fails to consider that Brennan et al. cannot be used against applicants' claims. This being so, the USPTO is attempting to render applicants' claims obvious over Harris et al. and Smith et al. The claimed method recites the administration of a TNF-antagonist selected from the group consisting of TNF receptor and a chimeric antibody comprising a TNF receptor and the constant domain of an immunoglobulin molecule. The USPTO asserts that applicants are not entitled to any earlier filing date for TNFR:Fc fusions since such constructs are allegedly not enabled in the earlier filings. Applicants respectfully disagree. It is well=established law that an applicants for patent need not describe background information that is recognized to be the imputed knowledge of one of ordinary skill in the art. This being the case, construction of Fc fusions was known, and the ordinary artisan at the time the instant application was filed would have known how to make Fc fusions in general. See, for example, EP 315062 and WO 89/09622, each of which were published on May 10, 1989 and October 19, 1989, respectively.

Smith et al. disclose the cloning and expression of the claimed TNF receptor. This article was authored by one of the co-inventors of the instant application. However, applicants claim priority of Serial Nos. 07/523,635 filed May 10, 1990; 07/421,417 filed October 13, 1989; 07/405,370 filed September 11, 1990; and 07/403,241 filed September 5, 1989. Clearly, applicants are entitled to priority of at least as early as the 07/523,635 May 10, 1990 application. This entitlement antedates the Smith et al. article and removes it from being a reference.

Now having the Brennan et al. and the Smith et al. articles removed from being used against applicants' claims, the rejection can only be based on the remaining article by Harris et al. The USPTO states that Harris et al. teach the use of *cytokine inhibitors* for the treatment of rheumatoid arthritis. This general and broad disclosure, without more, cannot render applicants' claims as obvious. Indeed, Harris et al. do not even disclose or suggest using the claimed TNF antagonists. A comparison of applicants' claimed priority documents with the Harris et al. article is irrelevant since Harris et al. can be overcome simply by comparing it's disclosure with applicants' claims. Thus, notwistanding the claim to priority issue, Harris et al. does not render applicants' claims unpatentable.

Assuming, arguendo. that Harris et al.can be combined with Brennan et al., such combination still would not render the instant claims as having been obvious. Such a hypothetical combination would teach away from the claimed invention. Indeed, Brennan and Harris would have resulted in a suggestion to use an *anti-TNF antibody* of Brennan as a

potential cytokine inhibitor to treat rheumatoid arthritis (Harris). No mention or suggestion exists in either of the articles to use the claimed TNFRs to treat rheumatoid arthritis. It is well-settled patent law that the prior art must actually suggest or disclose the modification in order for obviousness to be properly established. See, for example, *In re Bell*, 26 USPQ 2d 1529 (Fed. Cir. 1993) wherein, citing *In re Rinehart*, 189 USPQ 143 (CCPA 1976) it was held:

> A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. [emphasis added]

Certainly, neither Harris et al. nor Brennan et al. provide any teaching within them selves to suggest using the claimed TNFRs to treat rheumatoid arthritis. Moreover, any extrapolation of Brennan/Harris to include the claimed TNFRs could only result from the improper use of the "obvious-to-try" reasoning. It is well-established law that "obvious-to-try" is not the proper standard of review under §103. Clearly, the USPTO;s express reasoning that the TNFRs and anti-TNF antibodies "operate by the same mechanism" illustrates the improper use of the ibvious-to-try reasoning. Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. §103

Claim 6 stands rejected under 35 U.S.C. §103 as allegedly being obvious over Brennan et al. in view of Harris et al., Capon and Hoogenboom further in view of Smith.

Applicants respectfully disagree for the same reasons as detailed in response to the previous rejection. Brennan et al., Harris et al., and Smith et al. each for its own reason, cannot be used against applicants' claimed invention.

Notwithstanding priority dates, Hoogenboom et al. is irrelevant to applicants' claimed method. Hoogenboom et al. disclose the construction of an anti-transferrin antibody : TNF chimeric antibody. The antibody is specific for the transferrin receptor. There is no Fc portion. There is no TNFR portion. There is no disclosure or suggestion to use TNF receptors as the binding domain of the chimeric antibody. Indeed, it is anti-transferrin *antibody* that becomes the binding domain. Hoogenboom et al. teach away from applicants' claims since it advocates use of anti-transferrin antibodies, as well as TNF, not the claimed TNF receptors, in the chimeric antibody.

Capon et al., do not disclose the use of the claimed TNF antagonists for treating TNF mediated inflammation. Capon et al. simply disclose the construction of a fusion molecule containing *LHR* and the constant domain of an immunoglobulin molecule. There is absolutely no disclosure or suggestion in Capon et al. of constructing a fusion molecule using a *TNF receptor*, or of using TNF antagonists to treat TNF-mediated inflammatory disease. The

disclosure lacking in Capon et al. is certainly not found in Hoogenboom et al., thus any combination thereof to establish a teaching of a TNFR:Fc is legally and scientifically improper. Indeed, the USPTO states that Capon doesn't mention "cytokines." However, the USPTO states that is why Hoogenboom was chosen. The USPTO is respectfully reminded that applicants are not claiming cytokine:Fc fusions. Rather, applicants are claiming the use of a specific cytokine receptor:Fc fusion protein. Cytokines and their receptors are very different proteins, disclosure concerning one cannot be extrapolated to the other.

From the rationale used by the USPTO, it is clear improper hindsight is being used. Even so, the hindsight combination of the references still fails to construct the claimed compounds. The USPTO asserts Capon generically teaches that blocking the ligand-ligand binding partner interaction is a strategy for drug development. While this is absolutely true, this is not a novel idea by Capon. Such a strategy has been known for years. But such a broad generic statement of strategy is wholely insufficient to establish any kind of motivation. Indeed, Capon state that "ligand binding partners fused to moieties that prolong the in vivo half life" are an object of Capon's invention. Apparently recognizing the overly broad deficiency of Capon, the USPTO has cited Hoogenboom to "teach the fusion of the TNFr ligand (TNF) to an immunoglobulin Fc." The USPTO goes further to assert:

> [t]hus, all one of ordinary skill in the art would have to do is substitute the binding partner for the ligand as explicitly recommended by Capon.

Applicants disagree with the USPTO's analysis. "Substituting the binding partner for the ligand" in Hoogenboom as recommended by the USPTO, is confusing since Hogenboom does not explain which moiety of its fusion is indeed the "ligand." However, since there are only two choices, such a replacement as envisioned by the USPTO would result in the following molecules:

TNFR:TNF (TNFR replacing the anti-transferrin antibody)

or

TNFR:anti-transferrin antibody (TNFR replacing the TNF)

As clearly shown, neither of the constructs supposedly obvious to one of skill in the art results in the claimed TNFR:Fc. Indeed, neither includes an Fc portion. The USPTO stated "Hoogenboom teaches the fusion of TNFr ligand (TNF) to an immunoglobulin Fc region." This statement is entirely incorrect as no Fc region is part of a fusion protein in Hoogenboom.

Further, the USPTO states that Capon et al. disclose "the use of many different hormones and growth factors. In short the reference provides teaching of a wide variety of different

receptors." This statement is incorrect for the simple fact that the claimed TNF antagonists do not belong to any of the groups listed by the USPTO. Indeed, TNFR is not a hormone, nor is it a growth factor. The equating of TNFR to these groups is inappropriate. The person having ordinary skill in the art would not have found applicants' claimed method obvious in view of Capon et al. The remaining articles are removed as references either by their irrelevant disclosures or as not being appropriate prior art. Withdrawal of the rejection is requested.

In summary, applicants' claimed invention is in condition for allowance and applicants respectfully request a favorable Action upon reconsideration.

Respectfully submitted,

Stephen L. Malaska
Registration No. 32,655

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Box After Final, Commissioner of Patents and Trademarks, Washington, DC 20231, on the date indicated below.

Date: July 17, 1995 Signed: Nancie M. Kertoon